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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,432	10/15/2001	Chen-Kun James Shen	08919-016003	3256

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EXAMINER

KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 04/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/977,432

Applicant(s)

SHEN, CHEN-KUN JAMES

Examiner

Sumesh Kaushal Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-63 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

The Preliminary amendment filed on 10/15/02 has been acknowledged.

Claims 1-32 are canceled.

Claims 33-63 are pending and are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (<http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm>). Each amendment document that includes a change to an existing claim, or submission of a new claim, **must include a complete listing of all claims** in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. Claims 33-36, 41-46, 51-53 and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record AR*) in view of Miller et al (Biotechniques 7(9):980-990, 1989 *ref of record AZ*)^{*}.

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Zhang teaches an expression vector comprising, a tissue specific ζ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). The cited art teaches a HS-40 enhancer element (NF-E2/AP1-II) which comprises the nucleotide sequence of SEQ ID NO:1 (**tctgagtca**) see page 8503, fig-1B, 3'NF-E2/AP1-II. The cited art further teaches a method of expressing p-HS40 (3'NF-E2/AP1-II)- ζ 597GH expression vector into isolated K562 erythroid cells. The K562 cells were transfected with expression vector and the expression of growth hormone was measured by GH assay and/or RNA primer extension assay (page 8503 fig 1 and 2). The cited art further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to **tctgagtca**) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3). However, Zhang does not teach a retroviral expression vector comprising a tissue specific ζ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site driving the expression of a growth hormone.

Miller teaches the making of a N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific ζ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang. One would have been motivated to do so because retroviral vectors

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has increased transfection efficiency as compared to plasmid base DNA transfection system. One would have reasonable expectation of success in doing so since making a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. In addition given the broadest reasonable interpretation to the method of expressing a transcript in a cell (*wherein the cell is an isolated cell in-vitro*) one would have reasonable expectation of success in infecting the cell in-vitro using the above described retroviral vector. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

2. Claims 37-40, 47-50, 54-57 and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record AR*) in view of Miller et al (Biotechniques 7(9):980-990, 1989 *ref of record AZ*) as applied to claims 33-36, 41-46, 51-53 and 58-59 above, and further in view of Jarman et al (Mol. Cell. Bio. 11(9):4679-4689, 1991; *ref of record AI*).

Zhang and Miller are discussed in detail above*.

Jarman teaches a major regulatory element upstream of the human α -globin gene cluster, which comprises nucleotide sequences that matches 99.9% and 99.6% to the nucleotide sequences of SEQ ID NO: 2 and 3 of the instant application (page 4684, fig-5; and *the attached PTO sequence search report*). However, the nucleotide sequences as taught by Jarman do not contain point a mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca).

A retroviral vector wherein the gene of interest encodes a tissue specific ζ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone has been found obvious to one ordinary skill in the art at the time of filing in view of Zhang and Miller (see sec. 1 above). It would have been further obvious to make a retroviral vector wherein the nucleotide sequences comprising the HS-40 enhancer region as taught by Zhang has been replaced by the nucleotide sequences as taught by Jarman. It would have been further obvious introduce a point mutation (gctgagtca to tctgagtca) in the HS-40 enhancer region (Zhang) into the nucleotide sequences as taught by Jarman. One would have been motivated to do so because changing gctgagtca to tctgagtca enhances the transcription of a gene of interest (GH) operably linked the mutated HS-40 enhancer, therefore increasing the production of GH in genetically engineered cells. One would have reasonable expectation of success in doing so, since making a point mutation and constructing a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. In addition given the broadest reasonable interpretation to the method of expressing a transcript in a cell (*wherein the cell is an isolated cell in-vitro*) one ordinary skill in the art would have reasonable expectation of success in infecting the cell in-vitro using the retroviral vector as describe above. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 51-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a transcript by introducing a viral expression vector into an isolated cell (as claimed), does not reasonably provide enablement for any method of expressing a transcript by introducing a viral expression vector into any and all cell types wherein the cell is in in-vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature Of Invention:

The invention relates to a method of gene therapy.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses any and all methods of expressing a transcript by introducing any viral expression vector into any and all cell types in-vivo. At best the instant specification disclosed the making of a transgenic mouse by microinjection of DNA fragments into the pro nuclei of fertilized mouse eggs in-vitro (spec. page 7, lines 1-12). The instant specification fails to disclose a single working example that establishes introduction of a

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viral vector into an animal (in-vivo) via any and routes of administration (systemic or local) that leads to the expression of any gene of interest.

State Of Art And Predictability:

The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998 *ref of record AU*; Verma et al Nature 389:239-242, 1997 *ref of record AV*, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with

the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the scope of the invention as claimed encompasses the expression of any and all genes of interest.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a

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genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals

Quantity Of Experimentation Required:

In instant case gene based therapies (*delivery of a gene of interest in-vivo and its desired expression*) are not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making any and all viral vector encoding the transcripts (as claimed) and the administration of the viral vector via any and all route of administration to target any and all cell types in-vivo, followed by evaluation of transduction and expression efficiencies.

Conclusion

No claims are allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be

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reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal

PATENT EXAMINER


SUMESH KAUSHAL
PATENT EXAMINER